Remarks

Claims 1, 5, 7, and 18 have been amended. Claims 1 and 7 were amended to state that the microparticles in the dry powder have an average particle size of greater than 10 microns and up to 20 microns. Support for this amendment can be found in the specification at least at page 2, lines 5, 10 and 21 and in Examples 1 and 2 (see Tables on pages 13 and 14). Claims 5 and 18 were amended to delete a duplicate word. No new matter has been entered by this amendment. Applicants believe that it is proper for the present amendment to be entered since it places the application in condition for allowance. Alternatively, entry of this amendment is proper since it places the claims in better form for appeal, does not raise any new issues, and does not require further consideration or search.

The claims

The claims define compositions for the nasal administration of a drug in a dry powder form, methods of using the composition, and devices for administering the compositions. The compositions contain microparticles with an average particle size of greater than 10 microns and up to 20 microns, formed of drug and a diketopiperazine excipient. This size range of the microparticles is necessary to control the depth of penetration by the microparticles into the nasal system. The aerodynamic properties of the microparticles within this size range, such as weight-to-drag ratio, promote deposition of the microparticles in the nasal cavity. A size below 10 microns could cause the composition to pass into the pulmonary region or mouth, resulting in a less efficient delivery of the drug and causing undesirable side effects with certain type of drugs,

e.g., bitterness in the case of an antihistamine. The claimed size range allows a lower dosage of drug to be administered, reducing systemic side effects, such as somnolescence, and avoiding the problem with bitter taste associated with some drugs, such as antihistamines (page 2, lines 2-16).

Rejection Under 35 U.S.C. § 103

Claims 1, 2, 4, 5, 7, 9, 12, 14, 15, 17, and 18 were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,503,852 to Steiner *et al.* ("Steiner"). Claims 3, 8, 10, 16, 20, and 21 were rejected under 35 U.S.C. § 103(a) as being obvious over Steiner, in view of U.S. Patent No. 5,690,954 to Illum ("Illum"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992); *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is ***rigorous*** application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175

F.3d 994 at 999 (Fed. Cir. 1999) (emphasis added). The references must themselves lead those of ordinary skill in the art to what is claimed, otherwise the claims are not obvious.

Steiner

Steiner discloses several drug delivery systems using diketopiperazines and their analogs to form microparticles encapsulating a drug to be delivered. The microparticles may be microspheres with diameters ranging between 0.1 and 10 microns (col. 4, lines 32-40), but not greater than 10 microns, as required by the amended claims. Steiner does not disclose drug delivery systems for nasal administration. While Steiner mentions that the microparticles can include a diagnostic imaging agent useful for imaging the nasal tract, these microparticles are administered orally or through a needle for intravenous administration (col. 13, lines 14-24 and col. 11, line 65 until col. 12, line 4 and col. 12, lines 20-22), not via inhalation. Additionally, these particles are administered in a solution or in the form of a tablet, not in a dry powder.

Steiner does not mention nor suggest a composition for nasal administration of microparticles having an average size of greater than 10 microns and up to 20 microns. In contrast, Steiner discloses administering smaller microparticles, with average diameters from 0.1 to 10 microns. This size range is ineffective for improving the nasal administration of drugs. Microspheres below 10 microns will pass into the pulmonary region or mouth, resulting in a less efficient delivery of the drug and cause undesirable side effects with certain type of drugs, e.g., bitterness in the case of an antihistamine. Thus, Steiner does not address any problems associated with nasal administration of drugs.

Further, Steiner teaches away from nasal delivery which requires adhesion to and uptake within the nasal region. Steiner's sole mention of the nasal tract is limited to parenteral or enteral administration of diagnostic microparticles for imaging the nasal tract. Imaging is the exact opposite of drug delivery. In diagnostic imaging, the object to be imaged is not taken up and is not distributed systemically in the body, while in drug delivery, the drug is absorbed by the nasal mucosa and is distributed systemically in the body. Thus Steiner does not provide the necessary motivation to one of ordinary skill in the art to modify its particles so that they are suitable for nasal administration. Therefore claims 1, 2, 4, 5, 7, 9, 12, 14, 15, 17, and 18 are not obvious over Steiner.

Illum

Illum is directed at improving the bioavailability of high molecular weight drugs that are administered to the nasal cavity for systemic delivery (see col. 1, lines 15-18 and col. 4, lines 3-5). Illum addresses the problems of decreased efficiency of nasal drug delivery due to rapid clearance of nasal sprays and inefficient drug absorption in the nasal cavity by designing a bioadhesive microsphere delivery system that contains absorption enhancers. The bioadhesive microspheres adhere to the nasal mucosa upon contact by forming a gel (col. 3, lines 2-9) and have improved bioavailability due to the presence of absorption enhancers which increase the bioavailability of the drug (col. 4, lines 6-12). The microparticles have a size between 10 and 100 microns (col. 6, lines 13-15). Illum does not disclose the inclusion of diketopiperazines in the delivery system.

The combined References

Neither Steiner nor Illum provides a person of ordinary skill in the art with the motivation to combine these references. Steiner discloses the delivery of small microparticles, which are not suitable for nasal administration in a dry powder form. Steiner's microparticles have sizes ranging from 0.1 to 10 microns. Steiner's sole mention of the nasal tract is limited to imaging the nasal tract through enterally or parenterally administered compositions in the forms of liquid or tablets. In contrast, Illum is directed to particles with larger diameters, ranging from 10 to 100 microns, which may be administered to the nasal mucosa for drug delivery. Illum's microparticles are bioadhesive and form gels upon delivery to a mucosal surface (col. 6, lines 15-16). There is no suggestion in Steiner to modify its particles so that they are larger. Further, there is no suggestion in Steiner to modify its particles so that they can be administered in a dry powder form to the nasal mucosa. Thus, one of ordinary skill in the art would not be motivated to combine Steiner with Illum.

Even if one of ordinary skill in the art combined Steiner with Illum, claims 3, 8, 10, 16, 20, and 21 would not be obvious. Illum does not cure the deficiencies of Steiner. First, Illum discloses a broad range of diameters for the particles and does not teach the selection of particles having a narrow size range of greater than 10 microns and up to 20 microns, as required by the amended claims. Second, Illum discloses that microsphere delivery system for drug delivery through the nasal mucosa must be both bioadhesive properties (i.e. form a gel upon contact with the mucosa) and contain absorption enhancers to increase the bioavailability of the drug to be delivered. In contrast, applicants have found a different drug delivery system, one which merely requires the

use of diketopiperazines and does not require the formation of a gel or the addition of absorption enhancers. Thus, claims 3, 8, 10, 16, 20, and 21 would not be obvious over Steiner in view of Illum.

Further, neither Steiner nor Illum disclose forming the microparticles by spray drying. Illum discloses forming microspheres by emulsion and phase separation methods, followed by chemical crosslinking (see col. 6, lines 22-67). Steiner discloses forming the microparticles via precipitation (see col. 9, line 55 until col. 10, line 9). Therefore the combination of Steiner with Illum would not make claims 20 and 21 obvious.

Allowance of claims 1-5, 7-12, 14-18, 20, and 21, as amended, is respectfully solicited.

Respectfully submitted,

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